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ABSTRACT

This introduction to basic principles of psychotropic drug use in developmentally disabled patients is intended to provide personnel working in the field with information on appropriate clinical use as well as potential risks. Presented in outline form, information is provided on five classes of psychotropic drugs: antipsychotics; antidepressants; antimanic agents; anti-anxiety drugs; and stimulants. For each of these classes the outline briefly covers general guidelines for use including specific psychiatric indications and target symptoms, mechanism of action, available products, dosing guidelines, pharmacokinetics, side effects, rational use of the particular category of medication, and a list of potential drug interactions. 31 references. (DB)

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# The John F. Kennedy Center

Colorado's University-Affiliated Program for Developmental Disabilities

**Monograph #102**

# An Outline on Psychotropic Drug Use in the Developmentally Disabled Patient

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## Preface

This outline is intended as an introduction to basic principles involved with psychotropic drug use in the developmentally-disabled patient. While it is by no means all inclusive, it should provide personnel working in the field with an understanding of the clinical use of psychotropic drugs and the potential risks involved with their use. The outline covers the following five classes of psychotropic drugs: antipsychotics, antidepressants, antimanic agents, anti-anxiety drugs and stimulants. For each of these classes, the outline will cover general guidelines for use including specific psychiatric indications and target symptoms. The outline will then briefly cover mechanism of action, available products and dosing guidelines followed by a section on pharmacokinetics. Pharmacokinetics may be simply defined as the study of what happens to a drug once it is ingested -- in other words, a study of the absorption, distribution and elimination of a drug. This is important in that these properties impact the onset and duration of action of a given drug. Following this will be a discussion of side effects, rational use of the particular category of medication and a list of potential drug interactions. It should be noted that these are potential interactions; not all have clinical significance. A final note is regarding the reference list for this outline. All of the information contained herein may be found in any of a variety of pharmacological texts and articles. For this reason, the outline is not internally referenced. At the end of the outline, I have provided a listing of general references which may assist the reader in learning more about a particular topic.

## I. Introduction

A. A "psychotropic drug" is any drug intended to affect behavior or produce an altering effect on the mind.

B. Classification of psychotropic drugs

1. Antipsychotics
2. Antidepressants
3. Antimanic agents
4. Antianxiety drugs
5. Stimulants

C. Choice of Medication

1. Accurate diagnosis is essential in determining whether or not drug use is appropriate and which category of drug may be most helpful in ameliorating symptoms. This may require both patient and family histories in addition to documentation of target symptoms. Often accurate diagnosis is extremely difficult in this population.

2. Some degree of trial and error may be required in determining the most appropriate drug for an individual.

3. Adverse neuropsychiatric effects of other medications should be considered as potential causes of behavior. Examples of medications include: anticonvulsants (especially phenobarbital), antihistamine /decongestants, muscle relaxants, sedatives, theophylline, analgesics, cimetidine, hormones.

4. Polypharmacy is to be avoided whenever possible. Polypharmacy may be defined very simply as "the use of more than one drug having the same therapeutic effect for the same purpose." This applies to all classes of medication, not just psychotropics. In terms of practical application, this means that two antipsychotics should never be used concurrently. On the other hand, a patient with acute mania may temporarily require both an antipsychotic and lithium. This is not true polypharmacy since these drugs have differing mechanisms of action.

   Much has been written about the problems associated with polypharmacy. Probably the best reason for avoiding polypharmacy is that it has never been proven to be safer or more effective than using a single agent at an adequate therapeutic dose. Use of multiple drugs clouds the situation, since it is difficult to evaluate which agent is effectively treating the patient's target symptoms or producing an adverse effect. Further, the potential for adverse drug interactions and additive side effects increases significantly. The end result is often a patient who is "snowed" rather than effectively treated. Polypharmacy also increases the chance for nursing error and patient noncompliance in addition to unnecessarily increasing the cost of therapy. Some of these same problems may occur when using combinations of various classes of medication; therefore, the goal is always to have patients taking as few drugs as possible.

## II. Antipsychotics

These drugs are also known as "major tranquilizers" or "neuroleptics".

A. Genèral guidelines for use

1. Indications for use

   These agents are primarily indicated for the relief of symptoms of psychosis including delusions, disordered thoughts, agitation, bizarre behavior and hallucinations. They do not alter the course of the illness.

2. Examples of conditions which may have a psychotic component

   - Schizophrenia, any subtype
   - Major depressive disorders with psychotic features
   - Bipolar disorder
   - Delirium and dementia with severe behavioral changes
   - Paranoid disorders
   - Organic mental disorders with severe behavior disturbances

   There has been only limited documentation justifying the use of these agents in non-schizophrenic conditions. Certain antipsychotics are also occasionally used for nonpsychiatric indications including treatment of nausea and vomiting, preoperative sedation and treatment of hiccups.

3. Target symptoms amenable to treatment

   Antipsychotics may be useful in controlling these symptoms whatever the cause. If a reversible cause is present, the rational approach is to eliminate the cause rather than to treat the symptoms. (As an example, consider behavioral symptoms which are drug-induced.) Antipsychotics rarely eliminate all target symptoms but do reduce their frequency and severity.

| Target Symptom | Relative Response % |
|---|---|
| | |
| Combativeness | 100 |
| Hyperactivity | 80 |
| Hostility | 75 |
| Tension | 74 |
| Negativism | 72 |
| Appetite | 65 |
| Accessibility | 65 |
| Sleep | 65 |
| Amicability | 65 |
| Dress | 61 |
| Hallucinations | 61 |
| Appropriateness of conversation | 57 |
| Sociability | 55 |
| Mannerisms | 55 |
| Participation in adjunctive therapy | 53 |
| Delusions | 52 |
| Self-mutilation | 45 |
| Affect | 39 |
| Orientation | 35 |
| Compulsiveness | 30 |
| Memory | 28 |
| Realistic planning | 23 |
| Judgment | 18 |
| Insight | 0 |

   Symptoms such as lack of insight, social withdrawal, poor self-care and lack of judgment generally do not respond. Drugs do not "normalize" behavior.

4. Antipsychotics are intended only as adjuncts to the total treatment program.

B. Mechanism of action

   It has been postulated that psychosis may relate to excess activity of the neurotransmitter dopamine in certain areas of the brain. Although no definite answers exist, it is known that antipsychotics block the action of dopamine on receptor cells in the brain. This in turn appears to alleviate some target symptoms.

   Because neurochemical systems in the brain are relatively complex, the blockade of dopamine may lead to relative imbalances in other neurotransmitters and thus to a number of side effects.

C. Available antipsychotic drugs and doses

1. Doses

| Drug | Generic Name | Approved Upper Limit | Approximate Equivalent Dose |
|---|---|---|---|
| Thorazine | Chlorpromazine | 2000mg/day | 100.0mg |
| Mellaril | Thioridazine | 800mg/day | 100.0mg |
| Serentil | Mesoridazine | 400mg/day | 35.0mg |
| Moban | Molindone | 400mg/day | 12.5mg |
| Loxitane | Loxapine | 250mg/day | 12.5mg |
| Trilafon | Perphenazine | 64mg/day | 10.0mg |
| Stelazine | Trifluoperazine | 60mg/day | 5.0mg |
| Prolixin | Fluphenazine | 60mg/day | 2.0mg |
| Navane | Thiothixene | 60mg/day | 5.0mg |
| Haldol | Haloperidol | 100mg/day | 2.0mg |
| Prolixin Decanoate | Fluphenazine | 100mg/wk | --- |
| Haldol Decanoate | Haloperidol | 300mg/mo | --- |

2. Use in children is not approved for most of these agents.

| Drug | Minimum Age |
|---|---|
| Trifluoperazine | 6 yrs. |
| Haloperidol | 3 yrs. |
| Thioridazine | 2 yrs. |
| Chlorpromazine | 6 mos. |

3. All antipsychotics are equally effective when given in equipotent doses. (See "approximate equivalent doses".) Since some variability exists in individual response, certain people will respond better to one antipsychotic than another. If a patient does not respond to one antipsychotic, a trial of a drug from another chemical class is indicated.

4. As a general rule, a dose of 300mg of chlorpromazine (or its equivalent) given daily by mouth is considered the minimum effective dose for psychotic adult patients. Patients with organic brain syndromes may be unusually sensitive to antipsychotics; therefore, lower initial dosages are recommended.

5. There is no evidence suggesting that the use of multiple antipsychotics provides any greater efficacy than use of a single antipsychotic at a comparable dose. Polypharmacy should be discouraged.

6. Megadoses of antipsychotics and "rapid neuroleptization" techniques may be useful in acutely agitated or refractory patients, but these techniques should be reserved for situations where the patient fails to respond to conventional doses.

D. Pharmacokinetics

1. The onset of antipsychotic effect is variable, but in general a period of 3-6 weeks may be required before significant improvement is seen.

2. Blood levels have generally not been well established as correlates of clinical effect. Blood levels may be useful in assessing noncompliance, bioavailability problems or toxicity.

3. Plasma half-lives of these drugs do not correlate well with biologic activity. More important is the attainment of steady state levels in the central nervous system due to tissue saturation. These drugs may be dosed once daily and are slowly eliminated.

E. Side Effects

1. Acute side effects

a) Central nervous system

- drowsiness
- seizures
- toxic
- psychosis
- temperature instability

b) Anticholinergic effects

- dry mouth
- urinary retention
- blurred vision
- constipation

c) Cardiovascular effects

- ECG changes
- hypotension (decreased blood pressure)

d) Endocrine effects

- breast enlargement
- galactorrhea (production of breast milk)
- disturbances in the menstrual cycle
- weight gain
- changes in sexual function

e) Extrapyramidal symptoms (EPS)

These side effects are caused due to a relative imbalance between dopaminergic activity and cholinergic activity in the brain. This leads to changes in motor function resulting in movement disorders. Typically these occur within the first four weeks of treatment and disappear over 3 to 4 months, although some cases may be persistent. These symptoms occur in 40-60% of those receiving antipsychotics. They include:

akathisia -- uncontrollable motor restlessness, especially of the lower extremities; inability to sit still; often confused with agitation.

pseudoparkinsonism -- masked face, mechanical movements, stiffness, "cogwheel" rigidity, tremor at rest.

dystonias -- jerking or spasticity of neck, facial and limb muscles.

akinesia -- lack of movement without rigidity, muscle weakness.

Drug-induced EPS are treated with antiparkinsonian or anticholinergic drugs such as:

| Generic Name | Trade Name | Dose |
|---|---|---|
| | | |
| Amantadine | Symmetrel | 100-400mg/day |
| Benztropine | Cogentin | 1-6mg/day |
| Diphenhydramine | Benadryl | 100-400mg/day |
| Procyclidine | Kemadrin | 10-20mg/day |
| Trihexyphenidyl | Artane | 1-10mg/day |

These may worsen the anticholinergic effects of the antipsychotics.

f) Miscellaneous side effects

- photosensitivity (sunscreens required)
- cholestatic jaundice (symptoms include malaise and yellowing of the skin or whites of the eyes)
- agranulocytosis (symptoms include fever, chills, weakness, fatigue, sore throat)

2. Chronic effects

a) tardive dyskinesia -- lip-smacking, tongue and jaw - movements, choreoathetoid movements of arms, legs and trunk

Characteristics:

- especially common in women or those with organic brain syndromes
- usually occurs with long-term use and high doses
- often irreversible and relatively untreatable

b) ocular and dermatologic effects

Characteristics:

- stellate pigment deposits in lens and cornea which have minimal effects on vision; retinal deposits which may produce visual impairment
- bluish or grayish areas of skin
- both most frequently associated with thioridazine (doses > 800mg/day)

c) recent literature has also suggested the possibility of the development of a tardive psychosis although this is as yet poorly established

3. Neuroleptic malignant syndrome

   a) characterized by fever, rigidity, tremors, fluctuation in consciousness, blood pressure, pulse

   b) usually occurs early in therapy or after a dosage increase

   c) treatment requires immediate drug discontinuation and use of supportive therapy, bromocriptine or dantrolene

4. Comparison of side effects

| Drug (Brand Name) | Extrapyramidal Side Effects | Sedation | Anticholinergic Effects | Hypotension |
|---|---|---|---|---|
| Aliphatic Phenothiazine | | | | |
| Chlorpromazine (Thorazine) | moderate | high | moderate | high (IM) moderate (PO) |
| Piperidine Phenothiazine | | | | |
| Thioridazine (Mellaril) | low | high | high | moderate |
| Piperazine Phenothiazine | | | | |
| Prochlorperazine (Compazine) | high | moderate | low | low |
| Trifluoperazine (Stelazine) | high | low | moderate | low |
| Fluphenazine (Prolixin) | high | low | moderate | low |
| Thioxanthenes | | | | |
| Chlorprothixene (Taractan) | moderate | high | moderate | moderate |
| Thiothixene (Navane) | moderate | moderate | low | moderate |
| Butyrophenone | | | | |
| Haloperidol (Haldol) | very high | very low | very low | low |
| Dibenzoxazepine | | | | |
| Loxapine (Loxitane) | moderate | moderate | low | low |
| Dihydroindolone | | | | |
| Molindone (Moban) | moderate | low | low | low |

F. Rational use of antipsychotics

1. All antipsychotics are equally effective when given in equipotent doses, but individual patients may vary in their responses to given agents. Choice of drug will be based on history of response. Relative side effect profile may also be important in choosing a medication.

2. The goal of therapy is initial control of symptoms followed by a - maintenance or minimal effective dose. Medication is usually continued for at least 6 months to 1 year following a psychotic episode and may be required on a chronic basis.

3. Tapering of antipsychotics

a) Considerations before initiating a taper: stability of current behavior, medical need for taperingdiscontinuation, duration of therapy, size of original dose.

b) Risks of tapering antipsychotics: withdrawal dyskinesias, acute withdrawal-induced behaviors, return of symptoms.

c) General guideline is to taper the dose by no more than 10- 20% of the total every 2 to 4 weeks. This may be adjusted according to the needs of the individual. Of essence is a quick response to any severe decompensation.

G. Drug Interactions

| Drug Interacting with Neuroleptics | Clinical Effect of Interaction |
|---|---|
| Anticholinergics | 1. Delayed onset of neuroleptic effect in acute oral dose<br>2. May alter neuroleptic blood levels<br>3. Increased anticholinergic effect<br>4. Possible increased risk of hyperthermia |
| Antacids<br>Kaolin<br>Pectin | 1. Oral absorption delayed |
| Narcotics | 1. Increased sedation<br>2. Analgesia augmented<br>3. Hypotension augmented<br>4. Respiratory depression augmented<br>5. Anticholinergic effects augmented by meperidine |
| Benzodiazepines | 1. Increased central nervous system sedation |
| Cyclic antidepressants | 1. Increased sedation<br>2. Increased hypotension<br>3. Increased anticholinergic effect<br>4. May increase clinical effect of neuroleptic |
| L-dopa | 1. May exacerbate psychosis<br>2. Decreased antiparkinson effect of L-dopa |
| Amphetamines | 1 May exacerbate psychosis |
| Barbiturates<br>Nonbarbiturate hypnotics | 1. Increased sedation<br>2. Decreased clinical effect of neuroleptic |
| Anticonvulsants | 1. May lower seizure threshold<br>2. AC's may exacerbate target symptoms |

## III. Antidepressants

A. General guidelines for use

1. Indications for use

These agents are primarily indicated for the relief of acute depression characterized by slow, insidious onset, weight loss, insomnia and psychomotor retardation or agitation. They are generally not used for reactive depressions which are self-limiting in nature or for mild depression which causes no significant morbidity. They may also be used for certain other psychiatric disorders such as panic attacks or attention-deficit disorder and physical conditions such as bed-wetting.

2. Examples of conditions where antidepressants may be useful:

Major affective disorders
- Bipolar disorder
- Major depression

Other specific affective disorders
- Cyclothymic disorders
- Dysthymic disorder
- Atypical affective disorders
- Schizoaffective disorder
- Situational depression
- Attention deficit disorder

3. Target symptoms amenable to treatment:

| Somatic | Psychological |
|---|---|
| chronic fatigue | sadness/dejection |
| chronic pain | anger/anxiety* |
| sleep disturbance* | low self-esteem |
| self-neglect | guilt |
| change in appetite* | loss of skills* |

* These symptoms may be particularly apparent in the developmentally disabled population.

B. Mechanism of action

1. It has been postulated that depression may relate to deficiencies of the neurotransmitters serotonin and/or norepinephrine in specific areas of the brain. Antidepressants may act to increase the concentrations of these neurotransmitters in one of two ways.

2. Antidepressants in the polycyclic category act by preventing the re-uptake of neurotransmitters by the neurons. Monoamine oxidase inhibitors inhibit enzymatic breakdown of these chemicals in the synapse.

3. Some investigators have attempted to correlate deficiencies in specific neurotransmitters with specific symptoms of depression. For example, deficiencies in norepinephrine have been correlated with psychomotor retardation and drowsiness, whereas deficiencies in serotonin are reputed to result in anxiety, sleep disturbance and psychotic symptoms. Theoretically, this would enable a clinician to choose an agent most appropriate for a given patient, but this has not proven useful in clinical practice.

C. Available antidepressant medications and doses

1. Polycyclic antidepressants

| Drug | Generic Name | Usual Oral Daily Use | Maximum Daily Dose |
|---|---|---|---|
| Ascendin | amoxapine | 150-600mg | 600mg |
| Desyrel | trazodone | 150-600mg | 600mg |
| Elavil/Endep | amitriptyline | 150-300mg | 300mg |
| Ludiomil | maprotiline | 150-300mg | 300mg |
| Norpramin | desipramine | 100-250mg | 300mg |
| Sinequan/Adapin | doxepin | 150-300mg | 300mg |
| Tofranil | imipramine | 150-300mg | 300mg |
| Aventyl/Pamelor | nortriptyline | 100-150mg | 150mg |
| Vivactil | protriptyline | 10-60mg | 60mg |

2. Monoamine oxidase inhibitors

| Drug | Generic Name | Daily Use |
|---|---|---|
| Marplan | isocarboxazid | 10-30mg/d |
| Parnate | tranylcypromine | 20-30mg/d |
| Nardil | phenelzine | 60-90mg/d |

3. Safe use of most antidepressants in children has not been established. Only imipramine is approved for use in bed-wetting and then only for children over 6 years of age.

4. Initially, an empirical dose of 50mg of amitriptyline or its equivalent is used, with dosage increases of 25mg every few days depending upon clinical response or occurrence of side effects.

5. All polycyclic antidepressants are equally effective when given in adequate therapeutic doses. Because of differing effects on neurotransmitters, side effect profile and patient-to-patient variability,

certain agents may be preferred for selected individuals.

6. Use of MAO inhibitors is generally limited to patients with atypical depressions, refractory depressions or those unable to tolerate polycyclic antidepressants.

D. Pharmacokinetics

1. The onset of antidepressant response may be seen fairly rapidly on certain target symptoms, but full antidepressant effects may not be seen for up to 4 to 6 weeks at therapeutic levels.

2. The use of blood levels may be helpful in assessing response to certain polycyclic antidepressants. Blood levels are best established for desipramine, imipramine, nortriptyline and amitriptyline; they remain questionable for other agents. Levels are not useful with MAO inhibitors.

3. Due to the long half-life most polycyclic antidepressants can be given as a single dose, usually 1-2 hours before sleep. (Protriptyline is the exception here and is given in the morning.) Divided doses are indicated only if side effects occur. MAO inhibitors are usually given in divided doses, preferably before 6 p.m. to avoid insomnia.

E. Side Effects

1. PCA's

a) CNS effects
- drowsiness, weakness, lethargy are common
- seizures may occur
- other CNS effects: exacerbation of mania, EPS, nightmares, psychosis

b) anticholinergic effects (similar to those seen with antipsychotics)

- common but treatable
- appear prior to onset of therapeutic effect and may affect compliance
- may be some benefit to newer agents such as trazodone, amoxapine, maprotiline

c) cardiovascular effects

- postural hypotension
- cardiac arrhythmias, especially on overdose

d) miscellaneous, infrequent reactions

- blood dyscrasias
- jaundice
- sexual dysfunction

e) Comparison of agents

| Drug Class<br>Drug | Biochemical Effects<br>(N) Norepinephrine<br>(S) Serotonin | Relative Frequency of Side Effects<br>Sedation | <br>Anti-Cholinergic |
|---|---|---|---|
| TRICYCLICS | | | |
| Amitriptyline | (N) 0<br>(S) + | High | High |
| Nortriptyline | (N) +<br>(S) + | Moderate | Moderate |
| Protriptyline | (N) -<br>(S) - | Very Low | Low |
| Imipramine | (N) +<br>(S) + | Moderate | Moderate |
| Desipramine | (N) +<br>(S) 0 | Low | Low |
| Trimipramine | (N) +<br>(S) 0 | Moderate | Moderate |
| Doxepin | (N) -<br>(S) - | High | Moderate |
| TETRACYCLICS | | | |
| Maprotiline | (N) +<br>(S) 0 | Moderate | Moderate |
| DIBENZOXAZEPINES | | | |
| Amoxapine | (N) +<br>(S) + | Low | Very Low |
| TRIAZOLOPYRIDINES | | | |
| Trazodone | (N) 0<br>(S) + | High | Very Low |

2. MAOI

a) hypertensive reaction

- characterized by headache, palpatation, nausea, flushing
- secondary to food/drug interactions

| Foods | Drugs |
|---|---|
| aged cheeses | decongestants |
| smoked fish, meats | stimulants |
| red wines | narcotics |
| broad bean pods | other antidepressants |
| yeast extracts | |

This list contains examples only. A complete list and careful patient education are required prior to use of these drugs.

b) orthostatic hypotension

c) CNS effects
- restlessness, agitation, insomnia

d) miscellaneous - blurred vision, GI complaints, sexual dysfunction

F. Rational Use of Antidepressants

1. All polycyclic antidepressants are equally effective when given at adequate therapeutic doses. Because of differing effects on neurotransmitters and differing side effect profiles, certain agents may be preferred for a given individual.

2. Antidepressants are usually continued for 6 months to 1 year following an episode, with maintenance therapy required for some individuals.

3. When discontinuing treatment, the dosage of a polycyclic antidepressant is usually reduced at a rate of 50mg of amitriptyline or its equivalent on a weekly basis. MAO inhibitors are normally tapered over 7 to 14 days.

4. Combinations of 2 or more polycyclic antidepressants are contraindicated, since they offer no advantage. Combined MAO inhibitor and PCA use is also generally contraindicated due to the risk of hypertensive crisis. Combined use may be justified in refractory patients, but the MAO inhibitor must be added to the PCA, not vice versa.

G. Drug Interactions

1. PCA's

| Drug interacting with antidepressant | Clinical effect of interaction |
|---|---|
| Cimetidine<br>Methylphenidate<br>Acetaminophen<br>Oral contraceptives<br>Chloramphenicol<br>MAO inhibitors | 1. Inhibits metabolism, increasing blood level and toxicity of antidepressants |
| Guanethidine<br>Clonidine | 1. Decreased antihypertensive effect<br>2. Decreased antidepressant effect |
| Quinidine | 1. Cardiac condition prolonged Procainamide |
| Methyldopa | 1. Increased agitation, tremor, tachycardia |
| Coumarin anticoagulants | 1. Increased bleeding |
| Neuroleptics | 1. Antidepressants may increase plasma level of neuroleptic |
| Phenytoin<br>Barbiturates<br>Nonbarbiturate hypnotics<br>Doxycycline<br>Carbamazepine | 1. Induces hepatic metabolism, decreasing clinical effect of antidepressants |
| Anticholinergic drugs | 1. Increased anticholinergic toxicity |
| Triiodothyronine<br>Lithium | 1. Possible potentiation of antidepressant effect |
| Epinephrine<br>Local anesthetic dissolved in epinephrine | 1. Hypotension augmented<br>2. Increased bleeding in nasal surgery |

2. MAOI

| MAOI Dietary Restrictions<br>High Tyramine Content-Not Permitted | |
|---|---|
| | **Examples** |
| Aged, matured cheeses (unpasteurized) | Cheddar, Camembert, Bleu, Swiss |
| Smoked or pickled meats or poultry | Herring, sausage, corned beef |
| Yeast or meat extracts | Brewer's yeast |
| Red wines | Chianti, burgundy, sherry,vermouth |
| Italian broad beans | Fava beans |
| **Moderate Tyramine Content-Limited Amounts Allowed** | |
| Meat extracts | Bouillon, consomme |
| Pasteurized light and pale beers | |
| Ripe avocado | |

(adapted from Murphy et al)

| MAOI Drug Incompatibilities | |
|---|---|
| **Generally Contraindicated:** | **Hazardous Potentiations** |
| Stimulants | Weight reducing or antiappetite drugs; amphetamines; cocaine |
| Decongestants | Sinus, hay fever, and cold tablets; nasal sprays or drops; asthma tablets or inhalants; cough preparations (or any products containing ephedrine, phenylephrine or phenylpropanolamine) |
| Antihypertensives | Methyldopa, guanethidine, reserpine |
| TCAs | Imipramine, desipramine, clomipramine |
| Amine precursors | L-dopa, L-tryptophan |
| Narcotics | Meperidine (pethidine) |
| (adapted from Murphy et al) | |

## IV. Antimanic drugs

These agents are primarily indicated for the acute treatment or prophylaxis of bipolar disorder or manic-depressive illness. Bipolar disorder is characterized by alternating periods of mania and depression.

A. Lithium

1. General guidelines for use

a) Examples of conditions where lithium may be useful:

Indications for use
- acute mania
- prophylaxis against bipolar illness
- major depression

Other uses
- schizoaffective disorder
- schizophrenia
- disorders of impulse control
- selfinjurious behavior

b) Target symptoms amenable to treatment include: grandiosity, decreased sleep, talkativeness, distractibility and hyperactivity in addition to symptoms of depression.

2. Mechanism of action

It is unknown precisely how lithium works to stabilize mood swings. Lithium appears to compete with sodium, potassium and calcium on the cell membranes of nerves. This in turn may result in significant effects on neurotransmitters.

3. Lithium preparations and dosage

a) Lithium preparations

| | | |
|---|---|---|
| Lithium carbonate | | |
| capsules | 300mg | (Eskalith, Lithionate) |
| tablets | 300mg | (Eskalith, Lithane) |
| SR tablets | 300mg | (Lithobid, Lithotabs) |
| | 450mg | (Eskalith CR) |
| Lithium Citrate | | |
| solution | 300mg/5ml | (Cibalith-S) |
| generics are also available | | |

b) Lithium is not approved for use in children under 12 years of age.

c) Lithium dosage is primarily determined by the use of blood levels. Doses of 300-4200mg daily may be required to maintain a therapeutic level depending upon the individual patient.

d) The average starting dose for lithium is 300mg twice daily.This will be increased by 150-300mg every 4-5 days until blood levels reach the therapeutic range.

e) No significant differences exist among lithium preparations. Sustained release preparations may be preferred for those with gastrointestinal or renal side effects.

4. Pharmacokinetics

a) Lithium is inherently a long-acting drug with a half-life of around 24 hours. Multiple daily doses are often used,since side effects are more frequent with large (>900mg)single doses.

b) Peak lithium levels occur 1-6 hours after a dose of conventional preparations or 4-12 hours after extended-release tablets.

c) Desirable serum levels are as follows:

| | |
|---|---|
| acute phase | 0.8-1.5 mEq/L |
| chronic therapy | 0.5-1.2 mEq/L |

These should be drawn 12 hours after the last dose.

d) Although toxicity is well-correlated with serum levels on an immediate basis, therapeutic effects take some time. As a rule, onset of effect is after 4-7 days at therapeutic levels with full effects in 10-21 days.

5. Side Effects

| Mild side effects | Acute toxicity |
|---|---|
| nausea | persistent vomiting |
| vomiting | severe diarrhea |
| diarrhea | muscle weakness |
| anorexia | gross tremor |
| frequent urination | joint pain |
| thirst | lethargy |
| fine tremor | confusion |
| weight gain | seizures |
| | ECG changes |

a) Many of the mild side effects are transient or can be managed by giving smaller, more frequent doses or a sustained release product.

b) Toxic side effects may occur in some individuals (particularly those with organic brain damage) at therapeutic levels but are well-correlated with levels above 1.5 mEq/L. Prompt dosage reduction is indicated.

c) Chronic lithium use may lead to hypothyroidism and kidney damage.

d) Safe use of lithium requires baseline and frequent monitoring of blood chemistry, urinalysis, thyroid function, kidney function and cardiac status (in high-risk individuals). Discontinuation of lithium may be necessary if significant changes are seen. Lithium levels should be checked every 1-2 months or in the following situations: intercurrent physical illness; symptoms of toxicity; changes in sodium intake or balance; changes in other medications

6. Rational use of lithium

   a) A clinical trial of lithium should consist of at least 4 to 6 weeks at therapeutic blood levels.

   b) Lithium therapy is generally continued for 4 to 6 months. Maintenance therapy may be required in some individuals, although up to 50% of individuals will have only one manic episode.

   c) Concurrent antipsychotic use may be required until stabilization occurs.

   d) Recent reports have suggested that a lithium withdrawal syndrome consisting of acute mania may occur, although traditionally lithium was stopped abruptly. No guidelines exist, but it would be advisable to taper lithium over 7-14 days.

7. Drug interactions

| Drug | Effect |
|---|---|
| diuretics (thiazide) | Decrease renal clearance of lithium |
| antipsychotics | May cause temporary encephalopathy in some individuals |
| antiinflammatory analgesics (e.g.,ibuprofen) | May decrease the renal clearance of lithium |

B. Carbamazepine (Tegretol)

1. General guidelines for use

   a) Indications for carbamazepine

      Approved uses
      - seizure disorders
      - trigeminal neuralgia

      Other uses
      - bipolar disorder
      - pain syndromes
      - episodic dyscontrol/aggression
      - self-injurious behavior

   b) Target symptoms are similar to those used with lithium.

2. Mechanism of action

   Believed to suppress nerve transmission in the limbic area of the brain, an area of the brain which controls emotion.

3. Available products and doses

   a) Products

      100mg chewable tablets
      200mg tablets
      (generics are now available)

   b) Doses range from 400-2000mg daily

c) The usual adult initial dose is 200mg twice daily. This may be increased by 200mg every 4-5 days until maximum therapeutic levels are obtained or a positive response is seen. Slow titration appears to decrease the incidence of side effects.

4. Pharmacokinetics

a) The half-life is variable but is probably about a day. Although single daily dosing is possible, most often divided doses are used.

b) Blood levels are well-established for use of carbamazepine as an anticonvulsant, but these have not been well-correlated with psychiatric effects. Blood levels are generally used due to the increased risk of toxicity at levels above 12 mcg/ml.

c) Onset is variable, but clinical effects are usually seen within 1 to 2 weeks of achieving therapeutic doses.

5. Side effects

a) Central nervous system

- dizziness, drowsiness, ataxia, confusion
- dose related
- may have undesirable effects on behavior or on seizures

b) Gastrointestinal effects (early effect or dose related)

c) Dermatologic effects

- pruritis and rash may be a transient effect or indicative of a severe allergic reaction (medical evaluation required)
- photosensitivity may occur

d) Hepatotoxicity (monitoring of liver function required)

e) Hematologic effects

- aplastic anemia and other symptoms of bone marrow suppression
- monitor CBCs weekly for the first month and monthly for at least 1-2 years
- symptoms include sore throat, bruising, etc.-- not dose-related

f) Other

- eye changes, hypotension, congestive heart failure, decreased sodium, kidney damage

6. Rational use of carbamazepine

a) Carbamazepine use should be reserved for patients in whom lithium is ineffective or contraindicated for use.

b) Although the overall efficacy rate is similar to or less than that of lithium, carbamazepine may be more effective for rapidly-cycling patients.

c) Carbamazepine is generally used for a duration of 4 to 6 months and then re-evaluated.

d) Guidelines for use in explosive disorder or self-injurious behavior are less well-established.

7. Drug interactions

| Drug | Effect |
|---|---|
| anticonvulsants | Alterations in carbamazepine metabolism or changes in levels of other anticonvulsants |
| lithium; antipsychotics | Potential for rare neurotoxic reaction |
| erythromycin | Increased carbamazepine levels |

C. Other agents with potential antimanic activity

- benzodiazepines (e.g. clonazepam - Klonopin)
- calcium channel blockers (e.g. verapamil - Calan)
- antipsychotics
- thyroid preparations
- divalproex (Depakote)
- clonidine (Catapres)

## V. Antianxiety drugs

A. General guidelines for use

1. Because of the relatively nonspecific symptoms of anxiety and the pervasiveness of anxiety as a symptom of other psychiatric disorders, the guidelines for use of these agents are less well-established, and the potential for misuse is higher.

2. Specific indications for use may include:

- generalized anxiety
- panic attacks (alprazolam)
- phobias
- sleep disturbance

There are also a number of medical uses such as preoperative sedation, seizure disorders or muscle relaxants.

3. Medication is indicated only for severe anxiety of long duration sufficient to interfere with ability to function.

B. Mechanism of action

Antianxiety drugs exert a generalized CNS depressant effect. Benzodiazepines inhibit the effects of norepinephrine, serotonin and gamma-aminobutyric acid in the limbic area of the brain, thus attenuating the anxious response.

C. Available antianxiety agents and doses

1. Benzodiazepines

| Drug | Oral Dosage Range | Dosage Forms |
|---|---|---|
| ANXIOLYTICS (Long-Acting) | | |
| Diazepam<br>Valium | 6-40 mg/day<br><br>SR Cap 15 mg | Tab 2, 5, 10 mg<br>Inj 5 mg/ml |
| Chlordiazepoxide<br>Librium<br>Libritabs<br>Various | 15-100 mg/day | Cap 5, 10, 25 mg<br>Inj 100 mg<br>Tab 5, 10, 25 mg |
| Clorazepate<br>Tranxene | 15-60 mg/day | Cap 3.75, 7.5, 15 mg<br>Tab 11.25, 22.5 mg |
| Prazapam<br>Centrax | 20-60 mg/day | Cap 5, 10 mg<br>Tab 10 mg |
| Clonazepam<br>Klonopin | 1.5-20mg/day | Tab 0.5, 1.0,<br>2.0 mg |
| ANXIOLYTICS (Short-Acting) | | |
| Halazepam<br>Paxipam | 60-160 mg/day | Tab 20, 40 mg |
| Oxazepam<br>Serax | 30-120 mg/day | Cap 10, 15, 30 mg<br>Tab 15 mg |
| Lorazepam<br>Ativan | 2-6 mg/day | Tab 0.5, 1, 2 mg |
| Alprazolam<br>Xanax | 0.75-4 mg/day | Tab 0.25, 0.5,<br>1 mg |
| HYPNOTICS (Long-Acting) | | |
| Flurazepam<br>Dalmane | 15-60 mg | Cap 15, 30 mg |
| HYPNOTICS (Short-Acting) | | |
| Temazepam<br>Restoril | 15-30 mg | Cap 15, 30 mg |
| Triazolam<br>Halcion | 0.5-1.5 mg | Tab 0.25, 0.5 mg |

2. Other sedative/hypnotics

| Drug Class<br>Drug | Oral Dose | Dosage Forms |
|---|---|---|
| SEDATIVES<br>Barbiturates | | |
| Phenobarbital<br>Various | 15-30 mg bid-qid | Drops 16 mg/ml<br>Elxr 4 mg/ml<br>Tab 8,16,32,65,100 mg<br>Inj 30,65,130,163 mg/ml<br>Pwdr for Inj 65, 120, 130, 325 mg |
| Amobarbital<br>Amytal<br>Various | 30-50 mg bid-tid | Cap 65, 200 mg<br>Elxr 44 mg/5 ml<br>Tab 15,30,50,100 mg<br>Pwdr for Inj 250,500 mg |
| Propanediols | | |
| Meprobamate<br>Equanil<br>Miltown | 400 mg tid-qid | Cap 400 mg<br>Tab 200, 400, 600 mg<br>SR Cap 200, 400 mg |
| HYPNOTICS<br>Barbiturates | | |
| Pentobarbital<br>Nembutal<br>Various | 100-200 mg | Cap 30, 50, 100 mg<br>Elxr 20 mg/5 ml<br>Supp 30,60,120,200 mg<br>Inj 50 mg/ml |
| Secobarbital<br>Seconal<br>Various | 100-200 mg | Cap 50, 100 mg<br>Elxr 22 mg/5 ml<br>Supp 30,60,120,200 mg<br>Inj 50 mg/ml |

| | | |
|---|---|---|
| **Chloral Derivatives** | | |
| Chloral Hydrate<br>Noctec<br>Various Syrup | 500 mg-1.5 g | Cap 250, 500 mg<br>Supp 325,500,650 mg<br>250,500 mg/5 ml |
| Triclofos<br>Triclos | 1.5 g | Soin 100 mg/ml<br>Tab 750 mg |
| **Piperidinediones** | | |
| Glutethimide<br>Doriden | 500 mg-1 g | Cap 500 mg<br>Tab 250, 500 mg |
| Methyprylon<br>Noludar | 200-400 mg | Cap 300 mg<br>Tab 50, 200 mg |
| **Acetylinic Alcohols** | | |
| Ethchlorvyno<br>Placidyl | 1500 mg-1 g | Cap 100,200,500,750 mg |

3. Sedating antihistamines

| | | |
|---|---|---|
| diphenydramine<br>Benadryl<br>Various | 25-50 mg<br>tid-qid | Cap 25, 50 mg<br>Elxr 12.5 mg/15ml<br>Syrup 12.5 mg/5ml<br>Tab 25, 50 mg<br>Inj 10, 50 mg/m |
| hydroxyzine<br>Atarax<br>Vistaril<br>Various | 25-75 mg<br>tid-qid | Cap 25, 50, 100 mg<br>Syrup 10 mg/15ml<br>Tab 10,20,50,100 mg<br>Inj 25, 50 mg/ml |

4. Since the benzodiazepines are the most effective with the highest margin of safety, these agents are preferred and will be the only agents further discussed.

5. Choice of benzodiazepine relates largely to pharmacokinetic profile and approved indications, since all are effective as anxiolytics or hypnotics when used in appropriate doses.Cost should also be a consideration.

D. Pharmacokinetics

1. Comparison of agents

| Drug | Peak Oral Plasma Levels (Hours) | Half-Life (Hours) | Active Metabolites |
|---|---|---|---|
| clonazepam | - | 18-50 | no |
| diazepam | 1-2 | 20-50 | yes |
| chlordiazepoxide | 2-4 | 5-30 | yes |
| clorazepate | - | - | yes |
| prazepam | - | - | yes |
| halazepam | 1-3 | 7-14 | yes |
| oxazepam | 1-2 | 5-21 | no |
| lorazepam | 2 | 10-20 | no |
| alprazolam | 0.7-1.6 | 12-19 | yes |
| flurazepam | - | - | yes |
| temazepam | 2-3 | 9-20 | no |
| triazolam | 0.5-1.5 | 1.7-3 | yes |

2. Shorter-acting agents without active metabolites may be safest for geriatric patients or those receiving other medications, since accumulation and drug interactions are less significant.

3. Speed of onset may be especially important for use on an intermittent basis.

4. Blood levels are not well-established for these agents.

5. Due to the accumulation of active metabolites, full therapeutic effects may not be seen for several days, particularly with the longer-acting drugs.

E. Side effects

The overall incidence of side effects with these drugs is extremely low.

1. CNS effects

- frequently cause drowsiness, dizziness, muscle weakness, loss of coordination
- effects are dose-related and may decrease with time
- paradoxical rage or excitement may occur

2. Miscellaneous effects (rare)

- hypotension
- hepatotoxicity
- respiratory depression
- blood dyscrasias

3. Dependence potential

   a) It is difficult to predict, but generally dependence occurs in those receiving the drug for more than 3 months.

   b) Withdrawal reactions may cause agitation, mild physical complaints or seizures; therefore, gradual tapering over several weeks is essential.

F. Rational Use of Benzodiazepines

1. Treatment of generalized anxiety is generally effective but should be limited to short-term use. Benzodiazepines should not be considered as sole treatment.

2. Polypharmacy with benzodiazepines offers no therapeutic advantage.

3. In panic disorder, treatment is usually continued for at least one year. Chronic therapy may be required.

4. Benzodiazepines may be used as adjuncts to other psychotropic medications in the acute phase of various psychiatric illness.They should not be used on a continuous basis.

G. Drug interactions

| | |
|---|---|
| alcohol and other CNS depressants | Potentiation of depressant effect on central nervous system |
| cimetidine | Inhibition of benzodiazepine metabolism |
| anticonvulsants | Increased hepatic breakdown of benzodiazepines |

H. Buspirone (Buspar)

Buspirone is a new anxiolytic which differs chemically and mechanistically from the benzodiazepines. Although there has been little experience with this drug in the developmentally disabled population, it may offer some promise for those unable to take benzodiazepines or those with a history of drug dependence. Buspirone appears to be less effective in individuals with a past history of benzodiazepine use. Further information is needed to establish the place of this drug in therapy.

## VI. Stimulants

A. General guidelines for use

1. Specific indications for stimulants

   - narcolepsy
   - attention-deficit disorder
   - appetite control (short term)
   - depression (adjunctive therapy)

2. Target symptoms amenable to treatment in attention-deficit disorder: hyperactivity, irritability, attention to task, destructiveness. Target symptoms in depression: apathy and withdrawal.

B. Mechanism of action

These drugs stimulate the central nervous system including the cerebral cortex and subcortical structures. This may be a direct effect or due to inhibition of amine oxidase resulting in increases in neurotransmitters such as dopamine. This stimulant effect paradoxically produces a calming effect in those with attention-deficit disorder.

C. Selected stimulants and doses

1. Doses

| | |
|---|---|
| methylphenidate (Ritalin) | 10-60 mg/d |
| dextroamphetamine (Dexedrine) | 5-60 mg/d |
| pemoline (Cylert) | 37.5-112.5 mg/d |
| amphetamine (Benzedrine) | 5-60 mg/d |
| fenfluramine (Pondimin) | 40-120 mg/d |

2. Methylphenidate is used far more frequently than the other drugs. These agents are generally limited to use in patients unresponsive to methylphenidate.

3. Fenfluramine, an appetite suppressant, generated interest due to reports of utility in infantile autism. Results have been generally disappointing.

4. Initial doses are usually low with the dose increased every 1-2 weeks until a response is seen.

D. Pharmacokinetics

1. These agents have relatively short half-lives and are given in multiple daily doses. The last dose is always given before 6 p.m. to prevent insomnia.

2. Therapeutic effects do not correlate well with half-life.Effects are generally seen within one month of the start of therapy.

E. Adverse effects

1. CNS effects

- nervousness
- irritability
- insomnia
- paradoxical depression
- seizures

2. Cardiovascular effects

- palpitation
- hypertension
- tachycardia

3. Gastrointestinal disturbances

4. Tolerance, dependence and abuse may occur

5. Pediatric precautions - suppression of normal weight and height patterns

6. Miscellaneous reactions

   - hypersensitivity
   - hepatotoxicity

F. Rational use of stimulants

1. These drugs may be useful as adjuncts in the management of attention-deficit disorder. They are not the mainstay of treatment.

2. Patients may vary in degree of response to one stimulant versus another.

3. Periodic reassessments should take place for continuing need.Many adolescents can be successfully tapered off of medication,but a few cases of ADD, residual type, may continue into adulthood.

4. Stimulants are useful only for short-term treatment of mild depressions in withdrawn elderly patients. They may also be used in conjunction with antidepressants in refractory cases.

G. Drug interactions

| | |
|---|---|
| Acetazolamide (Diamox) | enhances amphetamine effect |
| Hydralazine | hypotensive effect may be inhibited |
| MAO inhibitors | mutual potentiation, possible hypertensive crisis, death |
| Meperidine (Demerol) | effect enhanced |
| Methyldopa (Aldomet) | decreased effect |
| Propoxyphene | increased CNS excitation; fatal convulsions may result |
| Sodium bicarbonate | increased amphetamine effect |
| Tricyclic antidepressants | increased amphetamine effect |

## VII. Conclusion

Psychotropic drugs may be a useful therapeutic tool in the care of the dually-diagnosed, developmentally disabled individual. They will not completely normalize behavior and should never be used in the absence of an appropriate psychiatric diagnosis. When used carefully with appropriate monitoring, these drugs may add significantly to quality of life for the dually-diagnosed.

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